Studies on the Syntheses of Heterocyclic Compounds. Part 683.† Stevens Rearrangement of Berbine Methiodides by Sodium Bis-(2-Methoxyethoxy)aluminium Hydride

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Refluxing berbine methiodides with sodium bis-(2-methoxyethoxy)aluminium hydride in dioxan resulted in Stevens rearrangements to afford spirobenzylisoquinolines and 8-methylberbines. The stereochemistry at the migrating carbon atom and the relationship between the configuration of the starting quinolizidinium salts and the products have been studied.

We have recently studied the hydrogenolysis of benzyl and allyl ethers and of quaternary benzyl- and allyl-amines [1] with sodium bis-(2-methoxyethoxy)aluminium hydride. In the course of this investigation, refluxing berbine methiodides with the metal hydride in dioxan was found to result in Stevens rearrangement to yield spirobenzylisoquinolines and 8-methylberbines. Kondo's [2] and Kano's groups [3] have recently reported the conversion of non-phenolic quaternary salts into spirobenzylisoquinoline with organometallic reagents and with lithium aluminium hydride, with retention of configuration at C-13a. However the stereochemistry at the migrating carbon atom and the relationship between the configuration of the quinolizidinium salt and the products have not yet been clarified.

Recently Yoshioka and his group determined the conformations of quaternary berbine alkaloids by ^{13}C n.m.r. spectroscopy.[4] Furthermore, (±)-canadine β-methiodide (1),[5] shown to possess a *trans*-quinolizidine conformation by ^{13}C n.m.r. spectroscopy in trifluoroacetic [^2H]-acid, showed its quaternary *N*-methyl signal at δ 2.83 in the ^1H n.m.r. spectrum [$(CD_3)_2SO$], whereas (±)-canadine α-methiodide (3), a *cis*-quinolizidine, exhibited the methyl signal at δ 3.22. On this basis the conformations of the quaternary berbine methiodides used for the following reactions were determined from the ^1H n.m.r. chemical shifts of the *N*-methyl groups [in $(CD_3)_2SO$].

Refluxing (±)-canadine β-methiodide (1) with sodium bis-(2-methoxyethoxy)aluminium hydride for 24 h gave the spirobenzylisoquinoline (6) (45%) and the 8-methylberbine (10) (33.3%). The spirobenzylisoquinoline (7) and the 8-methylberbine (11) were obtained (39.5 and 20.2%, respectively) from (−)-tetrahydropalmatine β-methiodide (2) [6] (*trans*-quinolizidine, NMe δ 2.83).

The methyl groups in the 8-methylberbines (10) and (11) were shown to have the β-configuration by spectroscopic analysis. Bohlmann bands in the i.r. spectra ($CHCl_3$) and the ^1H n.m.r. methyl signal at δ 1.50 ($CDCl_3$) are analogous with the properties of coralydine.[7,8] When the reaction was carried out in refluxing tetrahydrofuran, the extent of formation of the 8-methylberbines was decreased in comparison with that of the spirobenzylisoquinolines. Furthermore, the reaction of (±)-canadine β-methiodide (1) with lithium aluminium hydride in hot tetrahydrofuran furnished mainly canadine, in addition to a small amount of the spirobenzylisoquinoline (6).

On the other hand, treatment of (±)-canadine α-methiodide (3) with sodium bis-(2-methoxyethoxy)aluminium hydride in dioxan afforded the spirobenzylisoquinoline (6) (28%) and 3-(6-ethyl-3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-methylisoquinoline (14)[9] (45.1%). The 8-methylberbine was not detected. The structure (14) was confirmed by direct comparison with an authentic sample prepared according to the method reported.[9] Refluxing the methine base (15) with sodium bis-(2-methoxyethoxy)aluminium hydride also gave compound (14). Therefore (15) was considered to be an intermediate in the transformation into the isoquinoline (14). Because the H-13a in the *cis*-quinolizidine form is sterically more hindered than in the *trans*-form, it seemed that normal Hofmann degradation proceeded as the principal reaction although the occurrence of slow inversion at the quaternary nitrogen atom could not be discounted.

Treatment of coralydine [7,8] with methyl iodide in methanol gave a mixture of *trans*- and *cis*-quinolizidine methiodides, the n.m.r. spectrum of which showed two *N*-methyl signals at δ 2.79 (*trans*-) and 3.20 (*cis*). Only the *trans*-isomer (4) could be purified (by recrystallisation from methanol). Heating the *trans*-isomer (4) with sodium bis-(2-methoxyethoxy)-aluminium hydride in dioxan for 40 h yielded the spirobenzylisoquinoline (8) (30%) and the 8,8-dimethylberbine (12) (10%). The 8,8-dimethylberbine (12) was identical with material prepared by heating the phenolic isoquinoline (16) hydrochloride with acetone in acetic acid for 24 h to afford the phenolic berbine (13), followed by methylation with diazomethane.

Treatment of *O*-methylcorytenchirine,[7,8] the epimer of coralydine, with methyl iodide furnished the methio-

† Part 682, T. Kametani, M. Takemura, M. Ihara, and K. Fukumoto, preceding paper.

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[2] J. Imai, Y. Kondo, and T. Takemoto, *Heterocycles*, 1975, **3**, 467.

[3] S. Kano, T. Yokomatsu, E. Kamiyama, Y. Takagi, and S. Shibuya, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 1171.

[4] K. Yoshioka, I. Morishima, J. Kunitomo, M. Ju-ichi, and Y. Yoshida, *Chem. Letters*, 1975, 961.

[5] M. Tomita and M. Sugamoto, *J. Pharm. Soc. Japan*, 1962, **82**, 1141.

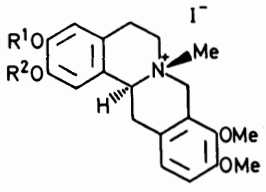
[6] M. Tomita and T. Kikuchi, *J. Pharm. Soc. Japan*, 1957, **77**, 73.

[7] S. T. Lu, T. L. Su, T. Kametani, A. Ujiie, M. Ihara, and K. Fukumoto, *J.C.S. Perkin I*, 1976, 63.

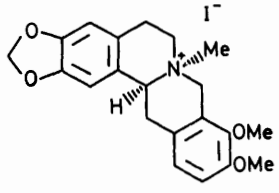
[8] T. Kametani, A. Ujiie, M. Ihara, K. Fukumoto, and S. T. Lu, *J.C.S. Perkin I*, 1976, 1218.

[9] I. Sallay and R. H. Ayers, *Tetrahedron*, 1963, **19**, 1397.

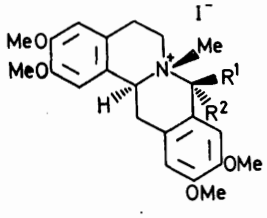
dide as predominantly one diastereoisomer, δ_{NMe} 2.98, indicating the *trans*-form (5). Treatment of (5) with the hydride reagent for 30 h yielded the spirobenzylisoquinoline (9) in 40% yield, but no berbine (12) was observed. The stereochemistry of the spirobenzylisoquinoline (8) and (9) was determined by the comparison of the chemical shifts of the 8-methyl groups [δ ($CDCl_3$) 1.33 for (8) and 0.95 for (9)]. Consideration of the effects on chemical shift due to ring A and to the nitrogen atom, the methyl groups of the spirobenzylisoquinolines (8) and (9) are thought to exist *syn* and *anti* to the nitrogen atom, respectively. Although the formation of trace amounts of



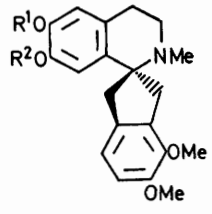
(1) $R^1R^2=CH_2$
(2) $R^1=R^2=Me$



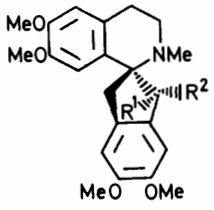
(3)



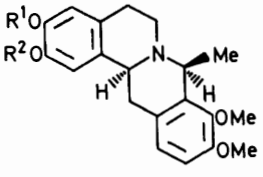
(4) $R^1=Me, R^2=H$
(5) $R^1=H, R^2=Me$



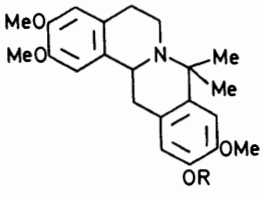
(6) $R^1R^2=CH_2$
(7) $R^1=R^2=Me$



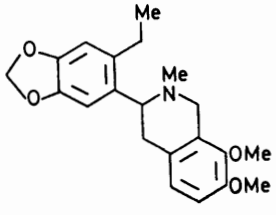
(8) $R^1=H, R^2=Me$
(9) $R^1=Me, R^2=H$



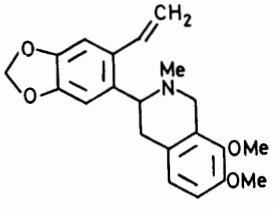
(10) $R^1R^2=CH_2$
(11) $R^1=R^2=Me$



(12) R = Me
(13) R = H



(14)



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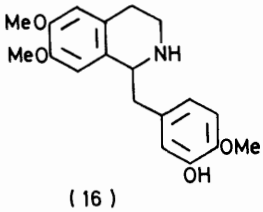

(16)

epimers were perceived by n.m.r. spectroscopic analysis of the crude products, the transformations of the berbine methiodides (4) and (5) into the spirobenzylisoquinolines (8) and (9), respectively, proceeded essentially stereospecifically with retention of configuration at the migrating carbon atom. Anionic [1,2] shifts would be expected to proceed with inversion at the migrating atom.[10] However, retention of configuration at the migrating atom in several Stevens rearrangements has been reported,[10] and this is a further example, the mechanism of which might involve a stepwise process.

[10] R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Verlag Chemie, Wienheim, 1970, p. 131, and refs. cited therein.

EXPERIMENTAL

I.r. and u.v. spectra were taken with a Hitachi 215 and a Hitachi 124 recording spectrometer, respectively. ^1H N.m.r. spectra were measured with a JNM-PMX-60 spectrometer. ^{13}C N.m.r. spectra were measured with a JNM-PS-100 spectrometer. Mass spectra were taken with a Hitachi RMU-7 spectrometer. A 70% solution of sodium bis-(2-methoxyethoxy)aluminium hydride in benzene (Wako Chemicals) was used for the following reactions.

(±)-*Canadine Methiodides* (1) *and* (3).—A mixture of canadine α- and β-methiodides [5] was washed with chloroform. The solid insoluble in chloroform was recrystallised from methanol to give (±)-*canadine β-methiodide* (1) as pale yellow hygroscopic crystals, m.p. 246—248° (Found: C, 51.35; H, 4.85; N, 2.8. $C_{21}H_{24}INO_4,0.5H_2O$ requires C, 51.45; H, 5.15; N, 2.85%), δ_H [$(CD_3)_2SO$] 2.83 (3 H, s, $\overset{+}{N}Me$), 3.80 (3 H, s, OMe), 3.83 (3 H, s, OMe), 6.03 (2 H, s, O·CH_2·O), 6.83 (1 H, s, ArH), 7.06 (1 H, s, ArH), and 7.10 (2 H, s, ArH), δ_C (CF_3·CO_2D) 26.078 (5-C), 30.929 (13-C), 41.367 (NMe), 57.869 (OMe), 63.684 (OMe), 64.482 (6- and 8-C), and 69.336 (13a-C).

The chloroform solution was evaporated and the residue was recrystallised from methanol to give (±)-*canadine α-methiodide* (3) as pale yellow crystals, m.p. 246—248° (Found: C, 52.45; H, 5.0; N, 2.85. $C_{21}H_{24}INO_4$ requires C, 52.4; H, 5.05; N, 2.9%), δ_H [$(CD_3)_2SO$] 3.22 (3 H, s, $\overset{+}{N}Me$), 3.82 (6 H, s, 2 × OMe), 6.03 (2 H, s, O·CH_2·O), 6.80

(1 H, s, ArH), 6.86 (1 H, s, ArH), and 7.03 (2 H, s, 2 × ArH).

Reaction of (±)-*Canadine* β-*Methiodide* (1).—A mixture of (±)-canadine β-methiodide (1) (1.25 g) and 70% sodium bis-(2-methoxyethoxy)aluminium hydride (7 g) in dry dioxan (70 ml) was heated under reflux with stirring in an oil-bath for 24 h under a current of nitrogen. The mixture was cooled, acidified with 10% hydrochloric acid, and evaporated. The residue was dissolved in water and washed with ether. The aqueous layer was neutralised with 10% ammonia and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give a gum, which was purified by silica gel column chromatography. Elution with benzene–methanol (99 : 1 v/v) afforded a solid, recrystallisation of which from ethanol yielded (±)-9,10-*dimethoxy*-8β-*methyl*-2,3-*methylenedioxy*-13aα-*berbine* (10) (305 mg) as crystals, m.p. 152—153° (Found: C, 71.45; H, 6.65; N, 4.05. $C_{21}H_{23}NO_4$ requires C, 71.35; H, 6.55; N, 3.95%), $\nu_{max.}$ ($CHCl_3$) 2 700—2 900 (Bohlmann bands) and 953 cm^{-1} (O·CH_2·O), δ_H ($CDCl_3$) 1.50 (3 H, d, *J* 6 Hz, 8-Me), 3.83 (6 H, s, 2 × OMe), 5.88 (3 H, s, O·CH_2·O), 6.57 (1 H, s, ArH), 6.73 (1 H, s, ArH), and 6.80 (2 H, s, 2 × ArH), *m/e* 353 (M^+), 178, and 176. Further elution with benzene–methanol (98.5 : 1.5 v/v) gave a solid, recrystallisation of which from ethanol yielded (±)-9,10-dimethoxy-2,3-methylenedioxyochotensane (6) (412 mg) as crystals, m.p. 117—118° (lit.,[11] 117—118°), $\nu_{max.}$ ($CHCl_3$) 935 cm^{-1} (O·CH_2·O), δ_H ($CDCl_3$) 2.26 (3 H, s, NMe), 3.83 (6 H, s, 2 × OMe), 5.79 (2 H, s, O·CH_2·O), 6.43 (1 H, s, ArH), 6.50 (1 H, s, ArH), and 6.80 (2 H, s, 2 × ArH), *m/e* 353 (M^+).

Reaction of (±)-*Canadine* α-*Methiodide* (3).—A mixture of (3) (48 mg) and 70% sodium bis-(2-methoxyethoxy)aluminium hydride (300 mg) in dry dioxan (3 ml) was heated for 24 h as above. Work-up gave a gum, which was subjected to preparative t.l.c. on silica gel with methanol–chloroform (1 : 9 v/v) and then methanol–ethyl acetate–benzene (1 : 4 : 5 v/v) as developer. The component of R_F 0.7 gave 3-(6-ethyl-3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-methylisoquinoline (14) (16 mg) as crystals, m.p. 99—100° (lit.,[9] 99.5—100°) (from ethanol), identical with an authentic sample prepared according to the reported method,[9] δ_H ($CDCl_3$) 1.17 (3 H, t, *J* 7 Hz, ArCH_2·CH_3), 2.20 (3 H, s, NMe), 2.66 (2 H, q, *J* 7 Hz, ArCH_2·CH_3), 3.36 (1 H, d, *J* 15 Hz, 1-H), 3.86 (6 H, s, 2 × OMe), 4.30 (1 H, d, *J* 15 Hz, 1-H), 5.89 (2 H, s, O·CH_2·O), 6.62 (1 H, s, ArH), 6.73 (2 H, s, ArH), and 6.97 (1 H, s, ArH). The component of R_F 0.5 yielded compound (6) (10 mg), identical with the sample described above.

Reaction of (−)-*Tetrahydropalmatine* β-*Methiodide* (2).—A mixture of (2) (300 mg) and 70% sodium bis-(2-methoxyethoxy)aluminium hydride (1.75 g) in dry dioxan (30 ml) was heated for 20 h under the same conditions as above. Work-up, followed by chromatography on silica gel in benzene–methanol (99 : 1 v/v), gave 2,3,9,10-*tetramethoxy*-8β-*methyl*-13aα-*berbine* (11) (45 mg) as crystals, m.p. 182.5—184°, $[\alpha]_D$ −235.5° (*c* 0.08 in MeOH) (Found: C, 71.35; H, 7.45; N, 3.75. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.35; N, 3.8%), $\nu_{max.}$ ($CHCl_3$) 2 700—2 900 cm^{-1} (Bohlmann bands), δ_H ($CDCl_3$) 1.53 (3 H, d, *J* 6 Hz, 8-Me), 3.83 (12 H, s, 4 × OMe), 6.60 (1 H, s, ArH), 6.73 (1 H, s, ArH), 6.79 (1 H, s, ArH), and 6.82 (1 H, s, ArH), *m/e* 369 (M^+), 192, and 178.

Further elution with benzene–methanol (98.5 : 1.5 v/v) afforded a solid, recrystallisation of which from ethanol yielded 2,3,9,10-tetramethoxyochotensane (7) (88 mg) as a gum, δ_H ($CDCl_3$) 2.36 (3 H, s, NMe), 3.59 (3 H, s, 2-OMe), 3.83 (9 H, s, 3 × OMe), 6.47 (1 H, s, ArH), 6.54 (1 H, s, ArH), and 6.82 (2 H, s, 2 × ArH), *m/e* 369 (M^+); the *hydrochloride*, recrystallised from methanol–ether, afforded pale yellowish crystals, m.p. 135—137° (Found: C, 60.9; H, 6.75; N, 3.25. $C_{22}H_{27}NO_4$,HCl,1.5H_2O requires C, 61.05; H, 7.2; N, 3.25%).

3-(2-*Ethyl*-4,5-*methylenedioxyphenyl*)-1,2,3,4-*tetrahydro*-7,8-*dimethoxy*-2-*methylisoquinoline* (14).—A mixture of 1,2,3,4-tetrahydro-7,8-dimethoxy-3-(4,5-methylenedioxy-2-vinylphenyl)-2-methylisoquinoline (15)[9] (70 mg) and 70% sodium bis-(2-methoxyethoxy)aluminium hydride (500 mg) in dry dioxan (5 ml) was heated for 24 h under the same conditions as before. Work-up gave a gum, which was purified by preparative t.l.c. on silica gel [methanol–chloroform (1 : 9 v/v)] to give compound (14) as crystals (46 mg), identical with an authentic sample [9] (t.l.c. and i.r. and n.m.r. spectra).

(±)-*Coralydine Methiodide* (4).—To a solution of coralydine [7,8] (1.7 g) in acetone (50 ml) was added methyl iodide (3 ml), and the mixture was set aside overnight. The precipitate (2.1 g) was filtered off and recrystallised from chloroform to give needles (900 mg), which were further recrystallised from methanol to yield the trans-*methiodide* (4) (500 mg) as needles, m.p. 253° (decomp.) (Found: C, 53.55; H, 6.2; N, 2.9. $C_{23}H_{30}INO_4$ requires C, 53.1; H, 6.0; N, 2.7%), δ_H [$(CD_3)_2SO$] 1.90 (3 H, d, *J* 7 Hz, 8-Me), 2.79 (3 H, s, $\overset{+}{N}$-Me), 3.81 (12 H, s, 4 × OMe), 6.91 (2 H, s, 2 × ArH), and 7.02, (2 H, s, 2 × ArH).

Reaction of (±)-trans-*Coralydine Methiodide* (4).—A suspension of (±)-*trans*-coralydine methiodide (4) (200 mg) and 70% sodium bis-(2-methoxyethoxy)aluminium hydride (2.5 g) in dry dioxan (20 ml) was refluxed with stirring under a current of nitrogen. The solvent was then removed and an excess of crystalline ammonium chloride was added to the residue. The mixture was extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated to leave an oil, which was subjected to preparative t.l.c. on silica gel [benzene–ethyl acetate–methanol (5 : 4 : 1 v/v)] to give the 8,8-dimethylberbine (12) (15 mg) as a syrup, δ_H ($CDCl_3$) 1.40 (3 H, s, 8-Me), 1.58 (3 H, s, 8-Me), 3.85 (12 H, s, 4 × OMe), 4.21 (1 H, dd, *J* 5.5 and 10 Hz, 13a-H), 6.54 (1 H, s, ArH), 6.57 (1 H, s, ArH), and 6.70 (2 H, s, 2 × ArH); the *hydrobromide* was recrystallised from methanol–ether to yield hygroscopic prisms, m.p. 246—247° (decomp.) (Found: C, 58.9; H, 6.55; N, 2.9. $C_{23}H_{29}NO_4$, HBr, 0.25 H_2O requires C, 58.9; H, 6.55; N, 3.0%).

The component of R_F 0.4 was extracted with chloroform–methanol (9 : 1 v/v) to afford the *spirobenzylisoquinoline* (8) (45 mg) as a gum, δ_H ($CDCl_3$) 1.33 (3 H, d, *J* 7 Hz, 8-Me), 2.26 (3 H, s, NMe), 3.54 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.87 (6 H, s, 2 × OMe), 6.46 (1 H, s, ArH), 6.53 (1 H, s, ArH), 6.69 (1 H, s, ArH), and 6.78 (1 H, s, ArH); *m/e* 383 (M^+), 368, 354, 206, and 178 (Found: C, 70.1; H, 7.6; N, 3.75. $C_{23}H_{29}NO_4$,0.5H_2O requires C, 70.4; H, 7.7; N, 3.55%).

(±)-O-*Methylcorytenchirine Methiodide* (5).—To a solution of (±)-*O*-methylcorytenchirine [7,8] (500 mg) in methanol (30 ml) was added methyl iodide (3 ml), and the mixture was set aside overnight. The solvent was evaporated off to leave a crystalline mass, which was recrystallised from methanol to afford the trans-*methiodide* (5) (600 mg) as pale yellow prisms, m.p. 212—215° (decomp.) (Found: C, 52.9; H, 6.35; N, 2.95. $C_{23}H_{30}INO_4$,0.5 H_2O requires C, 53.1; H,

[11] Y. Kondo, T. Takemoto, and K. Kondo, *Heterocycles*, 1974, **2**, 659.

6.0; N, 2.7%), δ_H [$(CD_3)_2SO$] 1.75 (3 H, d, *J* 7 Hz, 8-Me), 2.98 (3 H, s, $\overset{+}{N}$-Me), 3.80 (12 H, s, 4 × OMe), 6.86 (1 H, s, ArH), 6.90 (1 H, s, ArH), and 6.98 (2 H, s, ArH).

Reaction of (±)-trans-O-*Methylcorytenchirine Methiodide* (5).—A suspension of the methiodide (5) (200 mg) and sodium bis-(2-methoxyethoxy)aluminium hydride (2.5 g) in dry dioxan (15 ml) was refluxed for 30 h with stirring under a current of nitrogen. The solvent was removed and an excess of crystalline ammonium chloride was added to the residue, which was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated and the residue was subjected to preparative t.l.c. [benzene–ethyl acetate–methanol (2 : 2 : 1 v/v)]. The component of R_F 0.3 was extracted with chloroform–methanol (10 : 1 v/v) to give the spirobenzylisoquinoline (9) (60 mg) as a syrup, δ_H ($CDCl_3$) 0.95 (3 H, d, *J* 7 Hz, 8-Me), 2.48 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.89 (6 H, s, 2 × OMe), 6.36 (1 H, s, ArH), 6.57 (1 H, s, ArH), 6.68 (1 H, s, ArH), and 6.79 (1 H, s, ArH), *m/e* 383 (M^+), 368, 354, 206, and 178; the *hydrobromide* was recrystallised from methanol–ether to afford prisms, m.p. 251—252° (decomp.) (Found: N, 3.2. $C_{23}H_{29}NO_4$, HBr requires N, 3.0%).

(±)-2,3,10-*Trimethoxy*-8,8-*dimethylberbin*-11-*ol* (13).—A mixture of the phenolic isoquinoline (16) hydrochloride (440 mg) and acetone (2 ml) in glacial acetic acid (10 ml) was heated at 100 °C for 24 h. The excess of reagent and solvent were removed, and the residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a syrup, which was purified by chromatography on silica gel (10 g). Elution with benzene–methanol (99 : 1 v/v) gave a powder, which was recrystallised from benzene–n-hexane to afford the 8,8-*dimethylberbine* (13) (140 mg) as needles, m.p. 160—161° (Found: C, 71.5; H, 7.4; N, 3.7. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.35; N, 3.8%), $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1} (OH), δ_H ($CDCl_3$) 1.40 (3 H, s, 8-Me), 1.58 (3 H, s, 8-Me), 3.86 (9 H, s, 3 × OMe), 4.13 (1 H, dd, *J* 5.5 and 10 Hz, 13a-H), 6.58 (2 H, s, 2 × ArH), and 6.69 (2 H, s, 2 × ArH).

(±)-2,3,10,11-*Tetramethoxy*-8,8-*dimethylberbine* (12).—To a solution of the phenolic berbine (13) (60 mg) in methanol (30 ml) was added a solution of diazomethane in ether, prepared from nitrosomethylurea, and the mixture was set aside overnight. The solvent was evaporated off to afford the berbine (12) as a syrup, whose i.r. and n.m.r. spectra were identical with those of the foregoing sample. The hydrobromide was recrystallised from methanol–ether to yield prisms, m.p. 246–247° (decomp.), identical with the sample described before.

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